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Were it business opportunities or hidden risks: Observations on clinical trials and marketing authorizations of Gilead Science's remdesivir in China

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New drugs against the in COVID-19 pandemic are urgently needed. Gilead Science's remdesivir has been introduced to China through special approval procedures, and was directly conducting the Phase III clinical trial. As expected, the marketing authorization process was completed soon. The drug brought hope to patients as well as business opportunities to companies. However, we must pay attention to the patent competition, generic drug competition and other unfair competition that remdesivir may face in China. China also needs to strengthen the innovation ability and international cooperation ability of local pharmaceutical companies by taking advantages of the opportunity to introduce remdesivir.

1. Introduction

Remdesivir developed by Gilead Sciences Inc. is a nucleoside analogue and, as such, is a competitive inhibitor of RNA polymerase (RdRp) (Brown 2019). The nucleotide remdesivir-TP produced after metabolism can compete with RdRp. ATP can interfere with viral vRNA synthesis (Song 2019; Eastman et al. 2020). In *in vitro* cell studies and animal model experiments, remdesivir exerted antiviral activity against SARS-CoV and MERS-CoV (Omrani et al 2015; Sheahan 2017; De Wit 2020). At the same time, Gilead Science Inc. had tested the efficacy of remdesivir on Ebola patients in Libya and Guinea (Warren et al. 2016; Jordan et al. 2017; Sheahan et al. 2017). In February 2018, the FDA approved a clinical trial of remdesivir in patients with Marburg virus infection. In November 2018, the clinical trial of remdesivir on Ebola virus patients was approved (Agostini et al. 2018), it is expected to be completed in November 2023. Until very recently, the drug had no marketing authorizations in any region of the world, and its safety and effectiveness have not been confirmed. But since 2020, Remdesivir's fate has changed dramatically, becoming a hot star drug.

At the time of the COVID-19 outbreak, there were no specific drugs in worldwide. Hospitals could only provide some broad-spectrum antiviral drugs and immune-enhancing treatments (Hodgson 2020). Looking for more effective drugs to improve the treatment plan is the top priority in fighting the pandemic (Harrison 2020). According to some pre-clinical data of remdesivir in the treatment of SARS and MERS, the medical community suggested that remdesivir might have activity against COVID-19 (Gordon et al 2020) viruses. In January 2020, the first patient with imported COVID-19 appeared in the United States (Holshue 2020). On January 26, 2020, under the US Drug Compassionate Use System, doctors tried to inject remdesivir in patient. The fever symptoms greatly improved, and the blood oxygen saturation quickly recovered, so the patient did not longer need to inhale oxygen. In France, remdesivir was also used in the treatment of a patient with COVID-19, showing good results (Grein et al. 2020; Bhatraju et al 2020). These cases have greatly inspired the medical community. After the news spread to China, some Chinese medical experts called on the government to quickly introduce remdesivir to alleviate the high mortality rate of severe COVID-19 patients (Wang et al. 2020; Zhai et al. 2020). However, the problem was that remdesivir had not conducted any clinical trials in China, nor had it applied for drug marketing authorization. From the clinical trials to the final approval for marketing authorization, the entire process may even last more than ten years. Even according to the "Regulations on Response to Public Health Emergencies" (2003), the "Special Approval Procedure of the Chinese Food and Drug Administration" (2005), and the "Emergency Response Law"(2007), new drugs must comply with the principles of "standards would not lowered, procedures would not reduced." New drugs must be conducted not only for pharmacological and toxicological research, but also for three phases of clinical trials. Phase I clinical trials are conducted on healthy people to test whether the drug is safe. Phase II clinical trials are involving patients, demonstrate the effectiveness of the drug preliminary; the final phase III clinical trial aims at the patient to fully explore the effect of the drug on the disease. The clinical trials data must sound ideal before a drug is able to enter the final approval process. What broke this traditional procedure was the new "Drug Management Law" that came into effect on December 1, 2019. The Article 23 of this law stipulated: "For those drugs which can treat seriously life-threatening diseases, or drugs which can be used for some incurable diseases, and matched the public urgently needed in health, if the data in the mid-term clinical trials show the efficacy and can predict their clinical value, they can be conditionally approved and the relevant matters should be stated in the drug marketing authorization". Remdesivir had conducted phase I and phase II clinical trials against coronavirus (Jorgensen 2020), which was in line with the "clinical value" emphasized in the law, so it can be subject to conditional approval after the completion of phase III clinical trials. However, another problem faced by the introduction of remdesivir was that Phase I and Phase II clinical trials were conducted in the United States. Could clinical trials data obtained from foreign countries be accepted by Chinese officials? In the past, drug marketing authorization required clinical trials in China to address the sensitivity of different races to drugs. But now this restriction had been relaxed. According to

the "Provisions For Drug Registration" and other pharmaceutical policies, the Chinese National Medical Products Administration had approved the clinical trials data of remdesivir in foreign countries, making remdesivir skip Phase I and Phase II clinical trials, directly entering Phase III.

2. Clinical trials and hidden uncertainties of remdesivir in China

On February 2, 2020, the Drug Evaluation Center of the National Medical Products Administration approved two clinical trials of remdesivir against COVID-19: one was the "Randomized controlled clinical trial for patients with severe COVID-19" and the other was the "Randomized controlled clinical trial for patients with mild to moderate COVID-19". The applicants for the clinical trials were the Chinese Academy of Medical Sciences and the China-Japan Friendship Hospital of the Capital Medical University. The provider of clinical trial research contracts was Tiger Pharmaceuticals. The test sites were located in the Sino-French New City Campus of Wuhan Tongji Hospital, the West Campus of Wuhan Union Hospital, Wuhan Jinyintan Hospital, Wuhan Central Hospital, Wuhan Pulmonary Hospital, Wuhan University Central South Hospital, and Wuhan University People's Hospital. The drugs needed for these clinical trials were provided free of charge by Gilead Science Inc., which also supported the design and development of the study.

The start time of the "Randomized controlled clinic trial for patients with severe COVID-19 " was February 6, 2020, and it was expected to recruit 452 cases. The "Randomized controlled clinic trial for patients with mild to moderate COVID-19" started on February 5, 2020, and it was expected to recruit 308 cases. Both clinic trials were randomized, double-blind controlled, clinic trials conducted at 2:1, and two-thirds of patients in clinical trials had the opportunity to use remdesivir. The clinical trial inclusion criteria included "18 years of age or older", "chest imaging examination to prove lung infection", "the incidence of the disease does not exceed 12 days". The criteria for excluding participation in the trial include "severe liver disease", "known severe renal insufficiency", "received any experimental treatment drugs for COVID-19 within 30 days before the screening evaluation", etc.

According to the design plan of the clinical trials, the enrolled patients were be randomly assigned to the experimental group and the control group according to the time of onset or the severity of the illness. The results of the allocation would be blind to the subjects, medical staff, and experimental staff. The baseline of patients in clinical trials was basically the same, so as not to interfere with the results of clinical research. Based on the standard treatment regimen, the patients in the test group received the first dose of 200 mg remdesivir intravenously followed by 100 mg for nine consecutive days; the patients in the control group received standard treatment and the same dose of placebo. In terms of efficacy, the clinical trials set the main index and secondary index. The main outcome indexes refer to the decrease of the patient's temperature (axillary temperature ≤ 36.6 °C, or oral temperature ≤ 37.2° C, or anal temperature and ear temperature ≤37.8 ° C) within 72 h after drug used; the patient's respiratory frequency was maintained at ≤24 times/min; the patient's blood oxygen saturation reached more than 94%; the patient's coughing degree reached the stages "mild" or "no cough" (Chen 2020). If these indicators were met, it can be judged that remdesivir was effective. The secondary outcome indexes mainly included all-cause mortality, frequency of exacerbation of breathing, time to fever, time from dyspnea to mild or no breathing difficulty, frequency of requiring oxygen inhalation or noninvasive ventilation, upper respiratory tract samples COVID-19 PCR test to turn negative, the COVID-19 viral load reduction in the upper respiratory tract samples, the frequency of mechanical ventilation required, and the frequency of serious adverse events occurred in a time window of 28 days (Huang et al. 2020). If the patient was discharged within 28 days, a follow up meeting was scheduled after 28 days.

In terms of safety, the adverse reactions reported in the Phase I and Phase II clinic trials of remdesivir were mainly nephrotoxicity. In these clinical trials, the liver function and renal function of the patient would also be used as monitoring indicators of drug efficacy. According to the clinic trial plan, the clinical status of the subjects was followed up at four time points on the 7th, 14th, 21st and 28th days of the clinic trials.

Although the clinical trial plan sounded meticulous and rigorous, there were several aspects that to pay attention to during the clinical trial of remdesivir.

Firstly was the number of samples. Since the peak period of the COVID-19 epidemic in China appeared in early March, 2020 it had subsided rapidly. A large number of patients were cured and discharged, making it difficult to collect all the original clinical trial samples. At present, the hospital had disclosed that 270 patients have accepted remdesivir injection, but this had not yet reached the number required for clinical trial design. Another influential factor was that during this period, China had approved a total of more than 230 clinical trials on COVID-19 treatments, which would shunt some patients. At present, China's "Provision for Drug Registration" and "Management Standard of The Clinical Trial of Drugs " did not specify the impact of insufficient number of samples on the evaluation of the final results of clinical trials.

Secondly was the ethical review of clinical trials. On the one hand, there were always certain risks in clinical trials. Treating patients with new drugs may have better results or greater risks than existing therapies. The clinical trial must ensure that the person undergoing the trial had fully understood corresponding risks, and give them the right to withdraw at any time (Lachin 1981). In the clinical trials of remdesivir, risk notification faced difficulties because of the high contagious nature of the COVID-19, patients were strictly isolated and unable to see family members. Some patients even had a family infection and were treated in different hospitals. They were unable to obtain sufficient information about the drugs. Some severely ill patients were treated in the ICU ward and were unconscious. Some patients depended on ventilators and extracorporeal membrane oxygenation (ECMO) to maintain their lives (Wu and McGoogan 2020). According to the "Administrative Measures for the Development of Clinical Research Projects in Medical Institutions" issued by the China National Health Commission, all clinical trial projects must undergo ethical review, project declaration, and upload relevant information in the medical research registration information system. The ethics committee of the medical institution should independently conduct an ethics review. The hospital may hire independent experts to set up a data safety monitoring committee to evaluate the progress of clinical trial process, had the right to judge whether there were obvious toxic and side effects, or clear therapeutic effect, and report to the medical institution to terminate the trial. However, in this epidemic, the State Council of China issued a "Notice on Regulating Medical Institutions to Launch Clinical Research on COVID-19 Therapy", supported eligible hospitals to carry out clinical research on related drugs. It was also required that clinical research on COVID-19 drugs should insist on treatment priority and epidemic prevention priority, and should not affect or delay the treatment of patients because of research. This meant that clinical trials were no longer conducted independently by medical institutions and must be guided by the government. At present, the biggest uncertainty in the clinical trials of remdesivir was the problem of co-administration of multiple drugs. Patients with COVID-19, especially severely ill patients, accepted the cocktail therapy comprising multiple drugs at the same time (Zhou et al. 2020), even if the subject was receiving treatment with remdesivir, hospitals did not dare to stop other drugs. The control group sample did not dare to give placebo only during the trials, which made the final clinical trial results need to exclude some drug combination, which increased the difficulty of the clinic trials (Bornstein 2020).

Thirdly there was a double blind problem. The scientific design was that the subjects did not know which group they were assigned to, whether they were taking new drugs or placebo, and the experimenters were also completely unaware of all this (Jadad et al. 1996). At present, the efficacy of remdesivir had been widely reported in China. Some patients were eager to get treated with

remdesivir. The doctors were also paying close attention to it. The result was that both doctors and patients participating in the clinic trials knew more or less whether remdesivir was used or not. Some studies had shown that patients with mild COVID-19 could heal themselves with autoimmunity (Wu 2020). When the sample size was not large enough, some psychological cues may be formed, which may interfere with the clinic trail results. It should be acknowledged that this was a global problem. Recently, the World Health Organization announced the launch of a large global trial of "solidarity", using a randomized open controlled study method, that is, the trial was not blinded, patients and attending doctors were aware of the use of remdesivir, but the purpose of this trial was to screen drugs and should not serve as a pre-requisite for approval of drug marketing authorization (WHO 2020).

3. Subsequent possible risks for remdesivir in China

After the completion of clinical trials, the focus of the pharmaceutical industry was whether the drugs can be successfully marketed. In the future application process of remdesivir, the uncertainties likely to be encountered include the following aspects:

• How long did it take to marketing authorization?

After the clinical trials of new drugs, the normal approval process for marketing authorization takes more than a year. During the outbreak of SARS in 2003, the first specific drug approved by China, human anti-SARS-specific immunoglobulin, had completed clinic trials in July 2003. However, it was finally approved for emergency use only in August 2004. At this time, it remained to be seen whether the Chinese National Medical Products Administration can quickly approve remdesivir. If the normal marketing authorization approval process took too long, can China learn from the US system of Compassionate Use? In the treatment of the first newly diagnosed person with COVID-19 in the United States, the doctor weighed the risks and benefits and submitted a medication request to Gilead Science Inc. The medication was implemented with the support of the FDA. At least seven American patients are currently treated under Compassionate Use. China does not have this system currently. On December 20, 2017, the Chinese Food and Drug Administration issued the "Administrative Measures for Expanding Sympathetic Use of Drugs for Clinical Trials" (Draft for Comment), which stipulated that Compassionate Use drugs can only be applied under the following circumstances: a. The patient did not meet the conditions for enrollment and could not participate in the clinical trial of new drug; b. The patient cannot participate in clinical trials for new drug due to regional or time constraints. As can be seen from the regulations, the official attitude of China was still very cautious. Chinese Government did not want doctors to decide on their own to give non-marketing authorization drugs to patients, but rather wants doctors to solve the problem of emergency medication through risk controlled clinical trials. Moreover, this rule had not been officially adopted.

• Issue of patent competition

For an innovative drug, pharmaceutical companies can apply for multiple patents, such as screening compound structures, drug crystal forms, and usage of drug (Hemphill 2019). Gilead Science Inc. had already carried out patent layout on remdesivir. The earliest compound patent was WO2012012776A1 with an application date July 22, 2011. According to the PCT Agreement, Gilead Science Inc. had applied for patents in the United States, Japan, Europe, South Korea, and China. The grant date of Chinese patents was November 25, 2015, the validity period was 20 years. According to the data from the Chinese National Intellectual Property Administration, Gilead Scientific Inc. had applied for eight patents on remdesivir in China, three patents had been authorized, and five were under review. The scope of protection of these eight patent applications covered the core structure and similar structures and crystal forms of the compound, the manufacturing method, the pharmaceutical use for the treatment of coronavirus, etc. This time remdesivir showed certain effectiveness in the treatment of COVID-19, which aroused the interest of Chinese institutions. On January 21, 2020, the Wuhan Institute of Virology of Chinese Academy of Sciences announced that, in accordance with international practice and from the perspective of protecting national interests, it had already applied for "new uses of remdesivir against COVID-19" invention patents, and intended to enter the major countries of the world through the PCT Agreement. Our views were: first of all, although scientists had the freedom to apply for patents, they needed to make substantial contributions to the creativity, novelty and practicality of patents. The novelty of drug usage must meet at least the following three conditions. a. The new usage was substantially different from the original known use. b. The new usage was not directly inspired by the mechanism of action and pharmacological effects of the previously known uses. c. The new usage was not selective inventions that belong to the original known use. For example, the new use was narrower than the original use. The creativity of drug use meant that the new use of the drug cannot be clearly drawn or foreseen from the structure and compositions, molecular weight, known physicochemical properties of the drug itself and the existing use of the product must be based on new clinic trials and produced unexpected technical effects. The research that revealed effective of remdesivir was not the first published by Chinese scientists. The Chinese scientists had only repeated similar research on related drugs. Second, according to Article 25 of the Chinese "Law of Patent", no patent rights were granted for methods of diagnosis and treatment of diseases. The treatment time and dosage of remdesivir in the treatment of COVID-19 belonged to "treatment methods", and generally cannot be granted invention patent in China. Third, the Chinese scientific community and pharmaceutical companies had not invested in R&D of remdesivir and related compounds, had not mastered the core patents, and only applied for usage patents. Even if they were authorized in China, they can bring some restraint for the purchase of remdesivir in China, but Chinese patients would be very disgusted, and the government would not tolerate this. At the same time, due to the lack of innovation in some Chinese patents, it is difficult to obtain authorization in developed countries. Naturally, they cannot share the large global market of remdesivir, which will only cause patent friction.

• Will generic drugs of remdesivir be available soon?

If Remdesivir have been approved for marketing authorization or early listing based on conditions, whether China could use compulsory patent licensing to copy the new drug? Chinese "Law of Patent" stipulated that the National Intellectual Property Administration may grant compulsory licenses for the implementation of invention patents or utility model patents in the emergency or for the purpose of public interest. The "Measures for Compulsory Licensing of Patent" promulgated by the National Intellectual Property Administration stipulated that patent compulsory licensing should first examine whether to adopt patent compulsory licensing measures and make a decision. Before implementation, it should first actively seek authorization from the patentee. In 2018, the Chinese State Council issued the "Opinions on Reforming and Improving the Supply Guarantee and Use Policy of Generic Drugs", and also proposed the implementation of compulsory licensing of pharmaceutical patents to enable Chinese pharmaceutical companies to produce generic drugs. Some media also advocated Chinese Government to study and imitate Indian policy, allowing to copy effective but expensive drugs developed by some multinational companies. However, China was very cautious on this issue. So far, there had not been a single case of compulsory licensing of drug patents. Because China's pharmaceutical industry is different from India, and China has a much larger share of international trade than India, it also needed to assume more intellectual property obligations (Dunne et al. 2013).

• What unfair competition will be encountered?

On February 11, 2020, China's Borui Pharmaceuticals announced that they had mastered the synthesis technology and formulation technology of remdesivir APIs based on the compound structure disclosed in the remdesivir patent specification. The company already had the ability to mass-produce remdesivir APIs and hoped to cooperate with Gilead Science Inc. in the future to provide remdesivir intermediates or OEM production. China Hainan Phar-

maceutical Co., Ltd. announced that it had already produced the first batch of remdesivir preparations, with an annual production capacity of 3.5 million units. Hunan Warner Pharmaceutical Co., Ltd. also announced that it can manufacture remdesivir. Did these behaviors constitute unfair competition? On the one hand, Chinese companies using published patent information for product research did not need the permission of the patentee. If a new drug with a different chemical structure was developed on the inspiration of remdesivir, it was equivalent to bypassing remdesivir's patent protected range. On the other hand, China had established a drug trial data protection system. If remdesivir is approved for marketing authorization in China, generic drug manufacturers cannot use public data for drug development and production within the 6-year drug trial data protection period, they must rely on its own efforts to obtain drug trial data (Li et al. 2016). According to the provisions of the drug patent link, generic drug manufacturers can only do imitation only six months before the patent expired. According to the current patent situation, the core patents of remdesivir will expire as early as 2035. None pharmaceutical manufacturers can apply for generics before this. Even when the patent expires, the duration of drug data protection can play a role. According to China's generic drug declaration process, after expiration of drug trial data protection period, generic drugs can use public channels to obtain drug trial data , and carry out bio-equivalence and pharmaceutical equivalence trials to prove that generic drugs have the same efficacy and safety as the original drug, then they can apply for marketing authorization. In addition to this type of imitation, other imitation or trial production may constitute infringement.

4. Conclusion

The experience with remdesivir in China shows that accelerating drug marketing authorization approval according to the will of the government is a double-edged sword. Drug regulatory agencies in various countries need to find a balance between the necessity of drugs and public safety. If you bet on one drug and ignore the other, the damage caused will be huge. Therefore, everything needs to be based on science. At the same time, in the face of a sudden public health crisis, various countries, multinational companies and the host government need to fully communicate in legal rules, medical systems, R&D and medical expenses, and make reasonable arrangements to protect citizens' health right. It is also necessary to protect the virtuous circle of intellectual property and innovation.

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